

We claim:

1. An isolated human monoclonal antibody which binds to human CD89.

2. The isolated human monoclonal antibody of claim 1, wherein the antibody does not activate complement.

3. The isolated antibody of claim 1, wherein the antibody binds to CD89 at a site which is distinct from the IgA binding site of the receptor.

4. The isolated human monoclonal antibody of claim 1, wherein the antibody inhibits IgA binding to CD89.

5. The isolated human monoclonal antibody of claim 4, wherein the antibody inhibits IgA binding to CD89 by at least about 50%.

6. The isolated human monoclonal antibody of claim 1, wherein the antibody binds to human CD89 with an equilibrium association constant (K_a) of at least 10^8 M^{-1} .

7. The isolated human monoclonal antibody of claim 1, wherein the antibody binds to human CD89 with an equilibrium association constant (K_a) of at least 10^9 M^{-1} .

8. The isolated human monoclonal antibody of claim 1, wherein the antibody heavy chain is an IgG1 heavy chain and the antibody light chain is a kappa light chain.

9. The isolated human monoclonal antibody of claim 1 comprising a heavy chain encoded by the nucleic acid comprising the nucleotide sequence selected from the group consisting of SEQ ID NOs: 1 and 5 and a light chain encoded by the nucleic acid comprising the nucleotide sequence selected from the group consisting of SEQ ID NOs: 3 and 7, and conservative sequence modifications thereof.

10. The isolated human monoclonal antibody of claim 1 comprising a heavy chain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 2 and 6 and a light chain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 4 and 8, and conservative sequence modifications thereof.

~~11~~ An isolated human monoclonal antibody which binds to human CD89 and has at least one characteristic selected from the group consisting of:

(a) a binding equilibrium association constant (K_a) to human CD89 of at least about 10^7 M^{-1} ;

(b) a dissociation constant (K_d) from human CD89 of about 10^{-8} S^{-1} or less;

(c) absence of *in vivo* complement activation upon binding to human CD89;

(d) the antibody binds to an epitope on human CD89 which does not inhibit human IgA binding to the receptor;

(e) the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2 and 6 and conservative sequence modifications thereof, and a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4 and 8 and conservative sequence modifications thereof.

12. The isolated human monoclonal antibody of claim ~~1~~, wherein the antibody is a Fab fragment or a single chain antibody.

13. The isolated human monoclonal antibody of claim ~~1~~, wherein the antibody is produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene fused to an immortalized cell.

14. A hybridoma comprising a B cell obtained from a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene fused to an immortalized cell, wherein the hybridoma produces a detectable amount of a human monoclonal antibody according to claim ~~1~~.

15. The hybridoma of claim ~~14~~ selected from the group consisting of the hybridomas designated as 7.4, 8.2 and 14.1.

~~16~~ An isolated human monoclonal antibody which binds to an epitope on human CD89 defined by an antibody selected from the group consisting of mAbs 7.4, 8.2 and 14.1.

~~17~~ An isolated human monoclonal antibody which binds to an epitope on human CD89 defined by mAb 14.1 having a heavy chain amino acid sequence shown in SEQ ID NO: 2 and a light chain amino acid sequence shown in SEQ ID NO: 4.

~~18.~~ An isolated human monoclonal antibody which has the binding characteristics of an antibody selected from the group consisting of mAbs 7.4, 8.2, and 14.1.

5 ~~19.~~ An isolated human monoclonal antibody which has the binding characteristics of mAb 14.1 having a heavy chain amino acid sequence shown in SEQ ID NO: 2 and a light chain amino acid sequence shown in SEQ ID NO: 4.

10 20. A transgenic non-human animal which expresses the antibody of claim ~~1~~, wherein the transgenic non-human animal has a genome comprising a human heavy chain transgene and a human light chain transgene.

15 21. A method of producing an antibody of claim ~~1~~, comprising:
immunizing a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene with CD89 or a cell expressing CD89 such that antibodies are produced by B cells of the animal;
isolating B cells of the animal; and
fusing the B cells with myeloma cells to form immortal, hybridoma cells that secrete the antibody.

20 22. A bispecific or multispecific molecule comprising the human antibody of claim ~~16~~ and a portion which binds to a target antigen other than CD89.

25 23. The bispecific or multispecific molecule of claim ~~22~~, wherein the antibody is an Fab fragment or a single chain antibody.

24. The bispecific or multispecific molecule of claim ~~22~~, wherein the target antigen is a tumor antigen.

30 25. The bispecific or multispecific molecule of claim ~~22~~, wherein the portion that binds to the target antigen comprises an antibody or a tumor ligand.

26. The bispecific or multispecific molecule of claim ~~22~~ comprising a fusion protein.

35 27. The bispecific or multispecific molecule of claim ~~22~~ comprising a chemically linked conjugate.

28. The bispecific or multispecific molecule of claim ~~22~~ which induces lysis (ADCC) of a cell expressing the target antigen in the presence of effector cells expressing CD89.

5 29. The bispecific or multispecific molecule of claim ~~22~~, wherein the antigen is selected from the group consisting of carcinoembryonic antigen (CEA), gastrin releasing peptide receptor antigen (GRP), mucine antigens, epidermal growth factor receptor (EGF-R), HER2/*neu*, HER3, HER4, CD20, CD30, MAGE antigens, SART antigens, MUC1 antigen, c-erb-2 antigen and TAG 72.

10 30. A molecular conjugate comprising the human antibody of claim ~~16~~ linked to an antigen.

15 31. The molecular conjugate of claim ~~30~~, wherein the antibody is an Fab fragment or a single chain antibody.

32. The molecular conjugate of claim ~~30~~ comprising a fusion protein.

20 33. The molecular conjugate of claim ~~30~~ comprising a chemically linked conjugate.

34. The molecular conjugate of claim ~~30~~, wherein the antigen

25 35. A composition comprising the human antibody of claim ~~1~~ and a pharmaceutically acceptable carrier.

36. A composition comprising the bispecific molecule of claim ~~22~~ and a pharmaceutically acceptable carrier.

30 37. A composition comprising the molecular conjugate of claim ~~30~~ and a pharmaceutically acceptable carrier.

35 38. A composition comprising a combination of two or more human antibodies of claim ~~1~~, wherein each of said antibodies binds to a distinct epitope of human CD89.

39. The composition of claim ~~35~~ further comprising a cytotoxic agent.

40. An immunotoxin comprising the antibody of claim ~~2~~ linked to a cytotoxic agent.

5 41. A method of inhibiting growth of a cell comprising contacting the cell with an effective amount of the bispecific antibody of claim ~~22~~ such that growth of the cell is inhibited, wherein the bispecific includes a portion which binds to an antigen on the cell.

10 42. The method of claim ~~41~~, wherein the antigen is a tumor antigen.

43. The method of claim ~~42~~, wherein the tumor antigen is from a cancer cell selected from the group of cancers consisting of ovarian cancer, breast cancer, testicular cancer, prostate cancer, leukemia, and lymphoma.

15 44. The method of claim ~~41~~, wherein the antigen is an autoantigen.

45. The method of claim ~~41~~, wherein the antigen is from a microorganism.

20 46. The method of claim ~~45~~, wherein the microorganism is selected from the group consisting of a bacterium, a virus, and a parasite.

25 ~~47~~. A method of treating or preventing a disease characterized by precipitation of IgA-immune complexes, comprising administering to a subject in need of treatment an isolated human monoclonal antibody that specifically binds to CD89 in an amount effective to treat or prevent the disease, wherein the monoclonal antibody blocks IgA binding to CD89.

30 48. The method of claim ~~47~~, wherein the disease characterized by precipitation of IgA-immune complexes is selected from the group consisting of chronic hepatitis, Henoch-Schonlein purpura (HSP), Berger's disease, and IgA-glomerulonephritis.

35 49. The method of claim ~~47~~, wherein the monoclonal antibody binds to the epitope on CD89 defined by the antibody ~~8.2~~.

50. A method of detecting the presence of CD89 or a cell expressing CD89 in a sample, comprising:

contacting the sample with the antibody of claim ~~1~~ under conditions that allow for formation of a complex between the antibody and CD89; and

detecting the formation of the complex.

51. An expression vector comprising a nucleotide sequence encoding the variable and constant regions of the heavy and light chains of a human monoclonal antibody which binds to human CD89, wherein the heavy chain nucleotide sequence is selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 5 and the light chain nucleotide sequence is selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 7.

20120719 001